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Clobazam add-on therapy for drug-resistant epilepsy (Review)

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Bresnahan R, Martin-McGill KJ, Williamson J, Michael BD, Marson AG.
Clobazam add-on therapy for drug-resistant epilepsy.
Cochrane Database of Systematic Reviews 2019, Issue 10. Art. No.: CD004154.
DOI: 10.1002/14651858.CD004154.pub5.

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[Intervention Review]

Clobazam add-on therapy for drug-resistant epilepsy

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Editorial group: Cochrane Epilepsy Group
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 10, 2019.

Citation: Bresnahan R, Martin-McGill KJ, Williamson J, Michael BD, Marson AG. Clobazam add-on therapy for drug-resistant epilepsy. *Cochrane Database of Systematic Reviews* 2019, Issue 10. Art. No.: CD004154. DOI: 10.1002/14651858.CD004154.pub5.

ABSTRACT

Background

Epilepsy affects approximately 1% of the population, with up to 30% of patients continuing to have seizures, despite antiepileptic drug treatment. Clobazam is a 1,5-benzodiazepine and is commonly used as an add-on treatment for drug-resistant epilepsy. This review is an updated version of the original Cochrane Review, first published in 2008, and examines the most current literature regarding clobazam as an add-on for drug-resistant epilepsy.

Objectives

To assess the efficacy, effectiveness and tolerability of clobazam as an add-on therapy for drug-resistant generalised-onset and focal-onset seizures, with or without secondary generalisation, in adults and children.

Search methods

For the latest update, we searched the following databases on 9 October 2018: Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL), Medline (Ovid) 1946 to 8 October, 2018, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP). For some previous updates we also searched SCOPUS, DARE, and BIOSIS Previews, but these are no longer needed. (SCOPUS was searched as a substitute for EMBASE, but randomised and quasi-randomised controlled trials in EMBASE are now included in CENTRAL; DARE ceased operation at the end of March 2015; BIOSIS Previews yielded no relevant items that were not found in the other databases).

Selection criteria

Randomised trials of add-on clobazam, with adequate methods of allocation concealment, recruiting patients with drug-resistant focal or generalised-onset seizures, with a minimum treatment period of eight weeks.

Data collection and analysis

Two review authors independently selected trials for inclusion and extracted relevant data. The following outcomes were assessed: 50% or greater reduction in seizures, seizure freedom, treatment withdrawal and adverse events.

Main results

Four double-blind, placebo-controlled, cross-over studies, representing 197 participants, were included in the review. All four studies were assessed as having unclear risk of bias due to the unavailability of methodological details. The studies demonstrated significant method-

ological heterogeneity and differences in outcome measures were noted. Consequently, it was not possible to summarise the data in a meta-analysis. Instead, findings were summarised in a narrative data synthesis, Only two of the studies reported 50% or greater seizure reduction. They respectively reported that 57.7% and 52.4% of participants receiving add-on clobazam experienced a 50% or greater reduction in seizure frequency, although publication bias needs to be considered (2 RCTs, n = 47, very low-quality evidence). Seizure freedom was reported by three of the included studies. Collectively, 27 out of 175 patients were seizure-free during treatment with clobazam (3 RCTs, n = 175, very low-quality evidence). Two studies specifically stated that seizure freedom was not observed in any of the participants receiving add-on placebo. Treatment withdrawal was reported by all four studies. There was a slightly higher incidence of treatment withdrawal associated with receiving clobazam, although the overall incidence was still fairly low (4 RCTs, n = 197, very low-quality evidence). Adverse events were only described in two of the studies, reportedly 36% and 85% of participants experienced one or more adverse events whilst receiving clobazam. The most commonly reported adverse event was drowsiness.

Authors' conclusions

Clobazam as an add-on treatment may reduce seizure frequency and may be most effective in focal-onset seizures. It is important to recognise that this finding has been derived from very low-quality evidence and from studies judged to have an unclear risk of bias. It remains unclear which population demographic will best benefit from clobazam and over what time-frame. A large-scale, randomised controlled trial, conducted over a greater period of time, incorporating subgroups with differing seizure types, is required to effectively inform clinical practice.

PLAIN LANGUAGE SUMMARY

Clobazam as an add-on treatment in the management of drug-resistant epilepsy

Background
Epilepsy is a disorder of repeated seizures. Whilst many people will achieve freedom from seizures on one antiepileptic medication, some may require multiple medications to try to reduce the number of seizures that they have. These people are said to have drug-resistant epilepsy.

Aim of the review
Clobazam is an antiepileptic medication. Here, we examine the evidence from medical studies to determine how effective clobazam is at reducing the number of seizures that people have when used as an add-on treatment by people with drug-resistant epilepsy.

Results
We found four studies which had assessed clobazam as an add-on treatment for drug-resistant epilepsy. They included a total of 197 people. Two studies reported that more than half of the people given clobazam reached a 50% of greater reduction in the number of their seizures. Three of the studies reported how many people were seizure-free whilst taking clobazam. In total, approximately 15% of people were seizure-free when taking clobazam, compared to 0% when they were given placebo (a fake, inactive drug which should have no effect of epilepsy). All four studies reported how many people withdrew from treatment during the studies. Slightly more people withdrew from the studies when receiving clobazam (17 out of 197 people) than when receiving placebo (12 out of 197 people), but the rate of people withdrawing was still low overall. Clobazam was associated with side effects, in particular drowsiness.

All four studies were of short duration. They used different methods, e.g. different lengths of treatment, and were of poor quality. The results suggest that clobazam reduces seizure frequency for people with drug-resistant focal epilepsy (epilepsy that originates from one area of the brain), but there were not enough data to determine whether clobazam is as effective for generalised epilepsy (epilepsy involving the whole brain). The very low quality of the evidence provided by the four included studies means that we are very uncertain about whether the findings are accurate and, therefore, they must be taken and applied with caution.

The evidence is current to October 2018.

Summary of findings for the main comparison. Clobazam compared to Placebo in the management of drug-resistant epilepsy

Clobazam compared to Placebo in the management of drug-resistant epilepsy

Patient or population: children or adults with drug-resistant epilepsy
Setting: outpatients
Intervention: clobazam
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Clobazam				
50% reduction in seizure frequency Follow up (range): 9 weeks to 12 weeks	In both studies, more than half of the patients experienced a 50% or greater reduction in seizure frequency when receiving clobazam. One study reported that a significantly larger proportion of patients received a 50% or greater reduction whilst receiving clobazam, compared to placebo, whilst the other specifically reported that no patients receiving placebo experienced this outcome.		-	**47** (2 RCTs)	⊕⊖⊖⊖ **VERY LOW** [1, 2]	Clobazam may increase the likelihood of a 50% or greater reduction in seizure frequency but we are very uncertain.
Seizure Freedom Follow up (range): 8 weeks to 12 weeks	3 studies reported that multiple patients (27/175, collectively) achieved seizure freedom when receiving clobazam. Two studies specifically stated that no patients achieved seizure freedom when receiving placebo. One study did not report the incidence of seizure freedom amongst patients taking placebo.		-	**175** (3 RCTs)	⊕⊖⊖⊖ **VERY LOW** [1, 2]	Clobazam may increase the likelihood of achieving seizure freedom but we are very uncertain.
Treatment withdrawal Follow up (range): 8 weeks to 12 weeks	All 4 studies reported treatment withdrawal. 2 studies reported a higher occurrence of treatment withdrawal during the clobazam arm compared to the placebo arm (5/26 vs. 1/26 participants and 2/21 vs. 0/21 participants for each study, respectively), one reported a higher prevalence during placebo (11/129 vs. 10/129 participants). The fourth study did not specify which arm the patient was participating in when withdrawn.		-	**197** (4 RCTs)	⊕⊖⊖⊖ **VERY LOW** [1, 2]	Clobazam may slightly increase the risk of treatment withdrawal but we are very uncertain.
Treatment withdrawal due to adverse events Follow up: 12 weeks	Two studies reported incidence of treatment withdrawal due to AEs during the clobazam treatment arm (2/21 and 3/129). No patients withdrew due to AEs during the placebo arm.		-	**150** (2 RCTs)	⊕⊖⊖⊖ **VERY LOW** [1, 2]	Clobazam may increase treatment withdrawal due to adverse events but we are very uncertain.

50% reduction in generalised-onset seizure frequency Not measured	This outcome was not reported by any of the included studies and could not be calculated from the available data.	-	-	-
50% reduction in focal-onset seizure frequency Not measured	This outcome was not reported by any of the included studies and could not be calculated from the available data.	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Evidence was downgraded once with regard to the risk of bias domain because the included studies lacked methodological details leading to an unclear risk of bias judgement. No information was provided regarding funding.
[2] Evidence was downgraded once with regard to imprecision due to the narrative synthesis conducted and the subsequent absence of an estimated effect size. Evidence was downgraded again for imprecision because the number of events does not suffice the optimal information size.

BACKGROUND

This is an updated version of the Cochrane Review first published in 2008 (Michael 2008)

Description of the condition

Epilepsy is a common condition affecting 1% of the population. Although many advances have been made in the management of people with epilepsy, a significant proportion of the population, up to 30% in some studies, continue to experience seizures drug-resistant to even multiple combinations of antiepileptic drugs (AEDs) (Cockerell 1995). Whilst there is no unifying definition of 'drug-resistant' epilepsy, most definitions refer to continued seizures despite antiepileptic drug treatment. The generally employed definition is of continued seizures despite interminable medication changes (French 2006).

Description of the intervention

The 1,4-benzodiazepines, such as diazepam, have a clear role in the acute management of epileptic seizures. The 1,5-benzodiazepine clobazam has long been used as an add-on treatment to reduce seizure frequency (since having been initially investigated by Gastaut and colleagues in 1979, once it had come off patent (Gastaut 1979)).

How the intervention might work

Animal studies suggest that the difference in clobazam's chemical structure, and that of its active metabolite N-desmethyl-clobazam, give it a broader spectrum of antiepileptic activity, inhibiting the spread of seizures and increasing the seizure threshold, compared to the classical benzodiazepines. Further disadvantages to the use of 1,4-benzodiazepines, for example, the retention of diazepam in fat stores and the short half-life of lorazepam, are not encountered with clobazam as the half-life of the active metabolite is between 35 and 133 hours, resulting in a steady relative concentration of clobazam:N-desmethyl-clobazam of 1:8. Furthermore, there is retention of the diazepam ring following metabolisation (Robertson 1995).

Why it is important to do this review

Whilst concerns have been raised regarding the long-term use of clobazam, with regard to adverse events such as sedation and the development of tolerance, the only data to support these claims come from open, non-randomised trials, with widely ranging variation in the definition of 'tolerance'. The largest and most often cited trial was retrospective (CCCG 1991). Furthermore, the sedative, muscle-relaxant and behavioural effects are reported to be less marked than with diazepam and the other classical benzodiazepines (Kruse 1985). In addition, there has been some suggestion that, when used in conjunction with other AEDs, such as when managing cases of drug-resistant epilepsy, there may be additive efficacy without additive toxicity. This may, in part, be due to increased concentrations of the active metabolite, N-desmethyl-clobazam, due to the induction of hepatic enzymes by the other AEDs (Guberman 1998; Theis 1997).

The aim of this review is to examine the efficacy of clobazam as an add-on treatment in the management of drug-resistant cases of epilepsy, of focal-onset seizures, with or without secondary generalisation, and generalised tonic-clonic seizures, in both adults and children, with regard to seizure reduction, adverse events and tolerance.

OBJECTIVES

To assess the efficacy, effectiveness and tolerability of clobazam as add-on therapy for drug-resistant generalised-onset and focal-onset seizures, with or without secondary generalisation, in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

Studies were included if they satisfied the following criteria:

1. randomised studies with adequate methods of concealment of randomisation;
2. double-blind studies;
3. placebo-controlled
4. parallel group or cross-over studies;
5. have a minimum treatment period of eight weeks.

Types of participants

Children (< 16 years) or adults with drug-resistant generalised or focal-onset seizures (including simple focal, complex focal or secondary generalised seizures).

Types of interventions

1. The active treatment group received clobazam in addition to their usual antiepileptic drugs (AED) treatment.
2. The control group received placebo in addition to their usual AED treatment.

Types of outcome measures

Primary outcomes

Efficacy measures

1. Fifty per cent or greater reduction in seizure frequency

The proportion of participants with a 50% or greater reduction in seizure frequency in comparison to the pre-randomisation baseline period for the entire study population and for each of the seizure subgroups, partial-onset and generalised-onset, tonic-clonic seizures. This outcome was chosen as it is commonly reported in this type of study and can be calculated for studies that do not report this outcome, provided baseline data are recorded.

2. Seizure freedom

The proportion of participants achieving total cessation of seizures (all types).

Secondary outcomes

Effectiveness measures

1. Treatment withdrawal

The proportion of participants having their treatment withdrawn during the course of the treatment period, representing a measure of "global effectiveness". Treatment may be withdrawn due to adverse events, lack of efficacy or a combination of both.

Tolerability measures

1. Treatment withdrawal due to adverse events

The proportion of individuals experiencing adverse events requiring medication withdrawal.

2. Adverse events

The proportion of individuals experiencing any of the following adverse events, considered by the review authors to be common and important adverse events of antiepileptic drugs:

1. skin rash;
2. ataxia;
3. cognitive/behavioural;
4. sedation;
5. weight gain;
6. sleep disturbance;
7. other.

Quality of life measures

We summarised data on quality of life outcomes from any validated study in this review.

Tolerance measures

We summarised data on the development of antiepileptic drug tolerance, and the definitions used in each study, in this review.

Search methods for identification of studies

Electronic searches

Searches for the original Cochrane Review (Michael 2008) were run in March 2007. Subsequent searches were run in June 2010, February 2011, November 2012, January 2015, and April 2016. For this latest update the following databases were searched on 9 October 2018, with no language restrictions.

1. Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL), using the search strategy set out in Appendix 1.
2. Medline (Ovid) 1946 to 08 October 2018, using the search strategy set out in Appendix 2.
3. ClinicalTrials.gov, using the search strategy set out in Appendix 3.
4. WHO International Clinical Trials Registry Platform (ICTRP), using the search strategy set out in Appendix 4.

For the previous update, we also searched SCOPUS, DARE, and BIOSIS Previews, but these are no longer needed. (SCOPUS was searched as a substitute for Embase, but randomised and quasi-randomised controlled trials in Embase are now included in CENTRAL; DARE ceased operation at the end of March 2015; BIOSIS Previews yielded no relevant items that were not found in the other databases).

Searching other resources

In addition, we checked reference lists from the identified trials for other relevant articles.

Information about the searches carried out for the original version of this review ((March 2007) is in Appendix 5.

Data collection and analysis

Selection of studies

Two review authors independently assessed trials for inclusion. We compared results and resolved any disagreements by discussion.

Data extraction and management

We obtained the following information, where available, for each trial meeting our inclusion criteria.

Trial design

1. Sampling method
2. Inclusion and exclusion criteria
3. Method of diagnosis of epilepsy
4. Method of randomisation
5. Method of concealment of randomisation
6. Method of blinding
7. Method of tablet aesthetics matching
8. Stratification factors
9. Duration of baseline period
10. Duration of treatment period
11. Duration of 'wash-out' period in cross-over studies
12. Description of withdrawals and drop-outs

Patient factors

1. Age
2. Sex
3. How the diagnosis of epilepsy made
4. Seizure type(s)
5. Number and generic names of background AEDs
6. Seizure frequency prior to randomisation
7. Presence of neurological deficit/signs at baseline
8. Co-morbidities
9. Electroencephalogram (EEG) results at baseline
10. Neuroimaging computerised tomography (CT)/magnetic resonance imaging (MRI) scans

Treatment data

1. Medication dose per treatment group
2. Protocol for dosage increase and decrease
3. Total number of participants allocated to each group

Follow-up

1. The number of individuals in each group achieving a 50% or greater reduction in seizures per treatment group
2. The number of individuals in each group achieving total cessation of seizures
3. Where possible to ascertain, demographic factors and seizure types in relation to seizure reduction or cessation
4. The number of individuals having treatment withdrawn and reasons for withdrawal per treatment group
5. Participants missing in the data

6. For those excluded, the reason for exclusion, whether any of the excluded participants completed the treatment phase and whether any of those had a 50% reduction in seizure frequency during the treatment phase

Outcomes

Efficacy, tolerability, adverse events and tolerance, as listed above, per randomisation group.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias of the included studies using the 'Risk of bias' tool, as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Studies were assessed according to six parameters: method of randomisation, allocation concealment, method of blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias. For each parameter, studies were awarded either a 'low risk' of bias, a 'high risk' of bias or an 'unclear risk' of bias. Each judgment was justified by either a quote taken directly from the text or by a comment from the review authors, describing the study design, which led to the judgment being made.

Measures of treatment effect

We proposed to use risk ratios (RR) with 95% confidence intervals (CIs) to represent the primary and secondary efficacy outcomes. Alternatively, we intended to use 99% confidence intervals (CIs) to report the incidence of individual adverse events to permit multiple testing.

Unit of analysis issues

Cross-over studies introduce unit of analysis issues. Our intention was that if the cross-over study was well-conducted and methodologically sound, then the whole data set would be used. For those studies with problems, then only data from the first treatment period would be used.

Dealing with missing data

We planned to perform an intention-to-treat analysis of participants according to their treatment allocation, regardless of the final treatment that participants received. Consequently, participants not completing follow-up, or with inadequate seizure data, would have been considered to be non-responders. The intention-to-treat approach was still adopted for the descriptive analysis utilised.

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by comparing the distribution of important participant factors between trials (age, seizure type, duration of epilepsy, number of antiepileptic drugs taken at time of randomisation) and trial factors (randomisation, concealment, blinding and losses to follow-up).

We planned to assess statistical heterogeneity by using a Chi^2 test with the I^2 statistic where $P < 0.05$ indicates significant heterogeneity. Specifically, with regard to the I^2 statistic: 0% to 40% would have indicated heterogeneity which might not have been important, 30% to 60% would have possibly indicated moderate heterogeneity, 50% to 90% may have represented substantial heterogeneity, and 75% to 100% would have implied considerable heterogeneity. If heterogeneity had been found then potential causes would have been explored. In the absence of significant heterogeneity, we would have synthesised data using a fixed-effect model.

Assessment of reporting biases

We requested the trial protocol for each of the included studies to enable us to identify whether there had been any reporting bias with regards to the efficacy and safety outcomes of the studies. We proposed to investigate publication bias by examining funnel plots. This method was, however, hindered by the low number of studies identified for inclusion.

Data synthesis

In the case of low heterogeneity, as determined using the Chi^2 test, we originally proposed to use a fixed-effect model meta-analyses for data synthesis, using the Mantel-Haenszel risk ratio (RR) with 95% confidence intervals (CIs) . Where possible, we planned to analyse participants according to seizure type. Unfortunately, only one study provided data relevant to the efficacy outcomes, and consequently, we were unable to complete any meta-analysis. We instead employed a narrative data synthesis. Notably, for some outcome measures, a narrative interpretation of the data had already been planned; i.e. to summarise the data collected on tolerance and quality of life.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses according to age (children versus adults), seizure type (generalised versus focal-onset seizure) and severity at baseline (according to seizure frequency at baseline as this baseline characteristic is commonly reported). However, we were unable to execute any of the planned subgroup analyses.

Sensitivity analysis

We did not plan to conduct any sensitivity analyses.

Summarising and interpreting results

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to interpret findings, and GRADEpro GDT software (which imports data from Review Manager 5 software (GRADEpro GDT 2015)), to create a 'Summary of findings' table for the following outcomes, deemed to be the most important: 50% reduction in seizure frequency, seizure freedom, treatment withdrawal, treatment withdrawal due to adverse events, 50% reduction in generalised-onset seizure frequency, and 50% reduction in focal-onset seizure frequency.

Notably, the outcomes, 50% reduction in generalised-onset seizure frequency and 50% reduction in focal-onset seizure frequency, were not reported by any of the included studies and, therefore, could not be described in the narrative review. We still included both outcomes in the 'Summary of findings' table to remain transparent about these outcomes.

RESULTS

Description of studies

Results of the search

The search strategies used revealed a total of 349 records for potential inclusion. One hundred and eleven duplicate records were

removed. An additional 225 records were excluded due to their irrelevance. The full-text articles were obtained for the remaining 13 records to assess their eligibility for inclusion. We excluded another nine full-text articles for various reasons, as listed in Figure 1. Four studies remained eligible for inclusion in the review and were consequently used to formulate a descriptive analysis.

Figure 1. Study flow diagram.

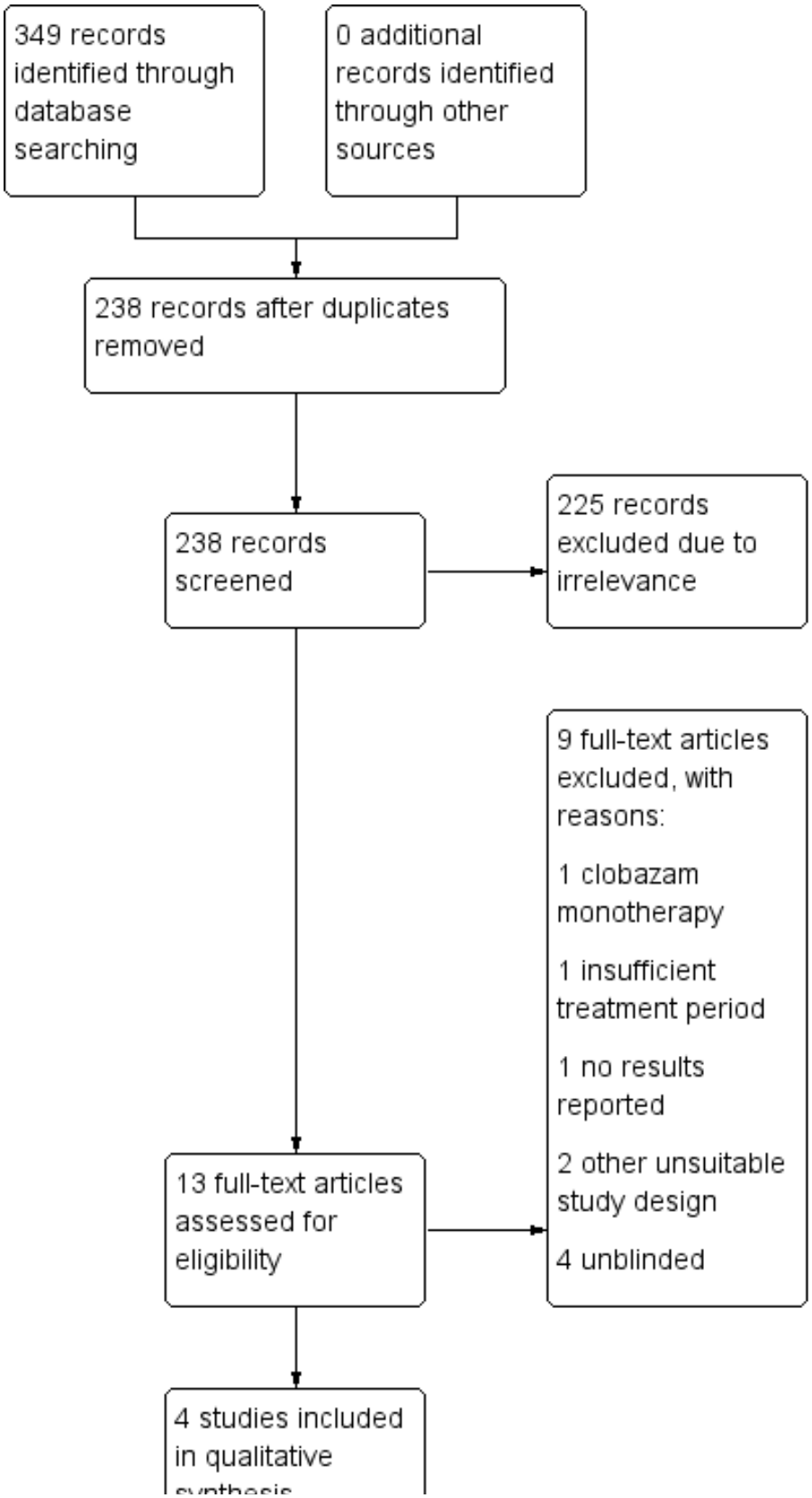
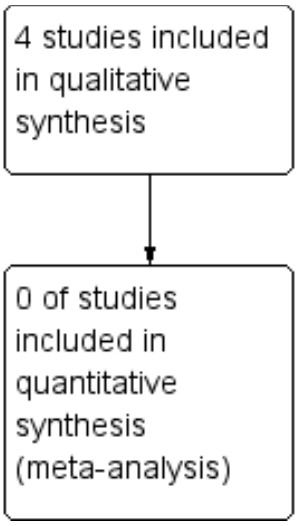


Figure 1. (Continued)



Included studies

The total number of participants included was 197. Details of the included studies are reported in the Characteristics of included studies table.

The study conducted by Allen 1983 was a double-blind, randomised, placebo-controlled, cross-over trial. The treatment/control period lasted nine weeks with an eight-week wash-out period between arms. The clobazam dosage employed was 30 mg at night for all participants, equivalent to 0.5 mg/kg, presuming a mean participant weight of 60 kg. The other AEDs being taken during the study period were carbamazepine, phenytoin, phenobarbitone and sodium valproate. The study sample size was limited with only 26 participants, of mean age 34 (range 18 to 60). The study included both participants with generalised- and focal-onset seizures, although the exact numbers of participants with each seizure type was not specified.

Keene 1990 was also a small, double-blind, randomised, placebo-controlled, cross-over study, recruiting 21 participants, aged 2 to 19 years (mean 11 years, number over 16 years undisclosed). At baseline, thirteen participants had generalised-onset seizures and eight had focal-onset seizures. Following an initial one-month baseline period, participants were assigned to a sequence of placebo-clobazam or clobazam-placebo. Treatment periods were of three months with a one-month wash-out period. The initial dosage of clobazam was calculated as 0.5 mg/kg on commencement, increased to 1 mg/kg if no response was achieved. Furthermore, were the participants to develop excessive drowsiness, the dosage was decreased by 0.25 mg/kg/day. Although they do state that baseline serum AED levels were taken and doses adjusted to achieve therapeutic levels, there is no report as to which AEDs were being taken at baseline.

The only multi-centre trial identified was conducted by Koeppen 1987 and took place across five European countries. This was also a randomised, placebo-controlled, cross-over study and was reported as being double-blind. This was the largest of the studies identified, recruiting 129 participants, of which, 63 were randomised to clobazam then placebo and 66 to placebo then clobazam. There was a one-month baseline period and each 'treatment' period was of three months duration with a one-month wash-out period. Clobazam doses ranged from 10 to 40 mg/day, equating to a dosage range of 0.17 to 0.67 mg/kg, presuming a mean participant weight of 60 kg. The baseline AEDs being taken were, in order of decreasing frequency: carbamazepine, phenobarbital, phenytoin, valproate and primidone. The baseline seizure types were 32 of generalised-onset and 149 of focal-onset, during the preceding year.

The fourth study, Schmidt 1986, was also a randomised, double-blind, placebo-controlled, cross-over study. The sample size was limited, involving only 21 participants aged between 18 and 55 years (mean 38 years). The dosage of clobazam used was 10 mg three times a day, increasing to a maximum of 40 mg three times a day in 10 mg increments in the first month. The maximum dose was continued for months two and three. Clobazam was then decreased by 5 to 10 mg stages over the 4th month. The placebo was increased and decreased following the same guide, thus creating a gradual wash-out period over one month. This resulted in a mean dose of 0.54 mg/kg (range 0.23 to 0.74 mg/kg). The study concluded with a one-month observation period, during which both clobazam and placebo were removed. The baseline AEDs being taken were, in order of decreasing frequency: phenytoin, carbamazepine, primidone, phenobarbital, valproic acid, mephenytoin and clonazepam. The baseline seizure types were six of generalised onset and 29 of focal onset. It was not stated if this was during the one-month observation period or another time-frame.

Excluded studies

A total of 9 studies (Andrade 2009; Basu 2007; Conry 2009; NCT02134366; NCT02564952; NCT02565108; NCT02726919; Semah 2014; Vajda 1985) were excluded from the review. The reasons for exclusions are provided in the Characteristics of excluded studies table.

During the initial search in March 2007, one study (Vajda 1985) was excluded. Despite the study being a randomised, controlled trial with cross-over design, investigating clobazam as an add-on for drug-resistant epilepsy, the study was a pilot study with only a three-day treatment period, followed by a longer-term cross-over study of only four weeks, with no wash-out period. It therefore, did not satisfy the inclusion criteria that specified that studies must have a minimum treatment period of eight weeks duration. Furthermore, only nine participants were randomised, of which, four were later transferred to an open trial. Only preliminary results were presented and these incorporated open, non-randomised participants. No standard follow-up period or outcome measures were described. Additionally, for the five participants in the randomised phase, no data were presented to determine seizure frequency or 50% reduction. The full study report was not published.

An updated search in November 2012 identified three additional studies (Andrade 2009; Basu 2007; Conry 2009) for potential inclusion.The studies were not, however, applicable for inclusion because: one study investigated as clobazam as a monotherapy (Andrade 2009), one was open-label and therefore did not suffice the blinding inclusion criteria (Basu 2007), and one had a treatment period shorter than 8-weeks in duration (Conry 2009)

An updated search in 2016 identified one further potentially eligible study (Semah 2014). This study was not applicable for inclusion because it was an open-label study and thus lacked any method of blinding.

During the latest update, the four studies, previously classified as ongoing studies (NCT02134366; NCT02564952; NCT02565108; NCT02726919), were reclassified as excluded studies. Notably, two of the studies (NCT02564952; NCT02726919) were identified to be open-label extension studies with single-group assignment, thus making the studies ineligible for inclusion in the review. Another study (NCT02134366) had been terminated due to recruitment issues, resulting from a limited target population. Consequently, there were no results available for inclusion in the review. For the remaining study (NCT02565108), we noted that both treatment groups received clobazam. The intervention treatment group received clobazam in combination with cannabidiol, whilst the control group received clobazam with add-on placebo. The study, therefore, did not satisfy the inclusion criteria.

Risk of bias in included studies

The results from the 'Risk of bias' assessment for the four included studies are summarised in Figure 2 and Figure 3. The individual do-

main ratings for each study can be found in the 'Risk of bias' tables, linked to the Characteristics of included studies tables. All four included studies were judged to have an unclear risk of bias, largely due to the incomplete reporting of the trial methodology, supplied in the full-text articles.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

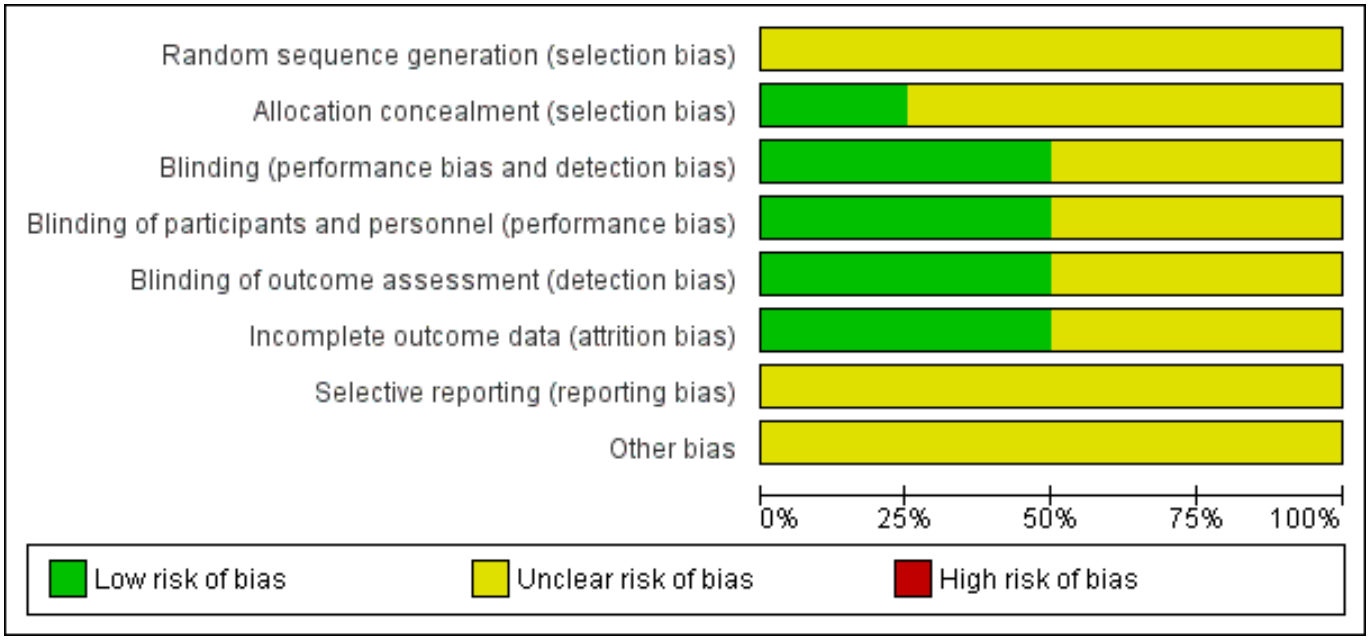
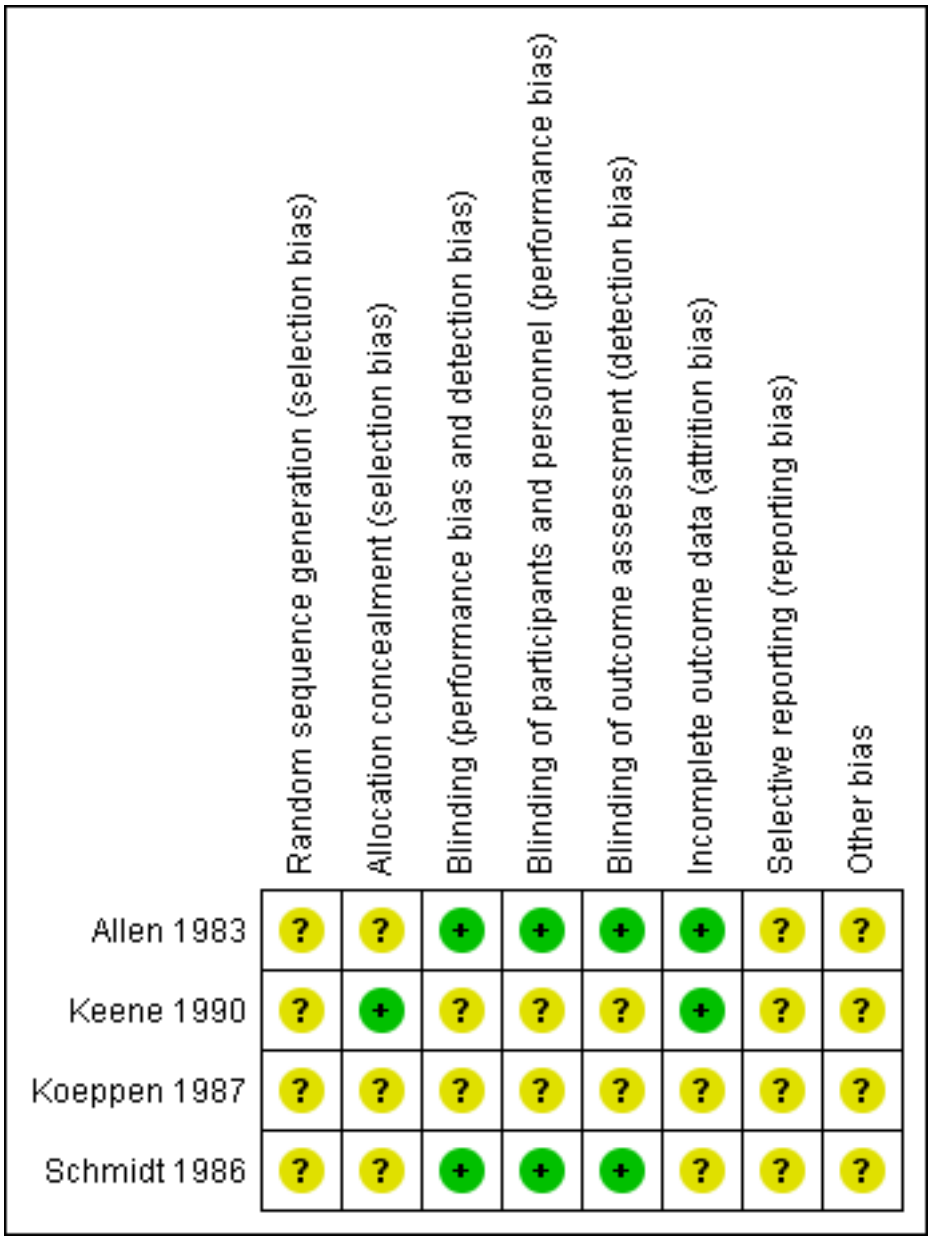


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Three of the included studies failed to adequately describe both the method used to generate the randomisation sequence, as well as the method for allocation concealment. The multicentre study by Koeppen 1987 reported that the randomisation method was different for each centre, however, the specific methods for each centre were not disclosed. All three studies were therefore awarded an unclear risk of bias for both parameters, random sequence generation and allocation concealment.In contrast, Keene 1990 did state that the hospital pharmacy was responsible for treatment allocation whilst a blinded pharmacist was responsible for dispensing the study drug and was thus awarded a low risk of selection bias. Keene 1990 did not, however, provide any details on how the randomisation sequence was generated and, consequently, we judged that Keene 1990 remained at unclear risk of bias for this domain.

Blinding

Two studies, Allen 1983 and Schmidt 1986, effectively described their methods of blinding. Matching placebo was given to participants to ensure the blinding of both participants and study personnel. In both studies, participants self-reported their seizure frequency and adverse events, and therefore, acted as the outcome assessors. As a result, the outcome assessors were, likewise, effectively blinded. Furthermore, study personnel, including those responsible for data entry and data analysis would, likewise, have been adequately blinded throughout their study involvement. The risk of bias for Allen 1983 and Schmidt 1986 was thus rated as low for both performance and detection bias. Conversely, Keene 1990 and Koeppen 1987 did not provide details of how the blinding of participants and study personnel was achieved. Both studies con-

sequently received an unclear risk of bias rating for performance and detection bias.

Incomplete outcome data

The risk of bias associated with attrition varied between the four studies. The study by Allen 1983 was judged to have a low risk of bias. Attrition was declared as the study reported that six participants withdrew during the trial. Additional analysis was carried out whereby all participants who withdrew from the study were included in the statistical analyses and were classified as non-responders,thus, intention-to-treat analysis had been performed. Similarly, Keene 1990 reported that two participants withdrew from the study. The results reported, however, included the total number of randomised participants, thus implying that intention-to-treat analysis had been conducted. Keene 1990 was likewise awarded a low risk of bias, with respect to attrition. In contrast, whilst Koeppen 1987 revealed that 21 participants withdrew from the study and another two participants provided incomplete outcome data, thereby reporting the attrition rate, Koeppen 1987 did not, however, compute efficacy data from these participants and, therefore, did not account for them in the analysis. As a result, intention-to-treat analysis was not performed and the study was deemed to have a unclear risk of attrition bias. Similarly, Schmidt 1986 reported that one participant was excluded from the study following randomisation, due to non-compliance regarding seizure count and tablet count. No information was provided as to which treatment group the participant belonged to when they were withdrawn, and moreover, the participant was excluded from any efficacy analysis. Consequently, intention-to-treat analysis was not conducted. Schmidt 1986 was, likewise, awarded an unclear risk of bias rating for attrition bias.

Selective reporting

All four studies (Allen 1983; Keene 1990; Koeppen 1987; Schmidt 1986) failed to supply a trial protocol for the 'Risk of bias' assessment. The four studies were judged to have unclear risk of bias with respect to selective reporting. Three of the studies, Allen 1983; Koeppen 1987 and Schmidt 1986, neglected to define any specific efficacy outcomes within the methods sections of their texts. It was therefore unclear whether all intended outcomes had been measured and reported within the respective results sections. In contrast, the remaining study, by Keene 1990, specified in the methods section of their article that their efficacy outcome of interest was a 50% or greater reduction in seizure frequency. The results for this outcome were then fully reported within the results section of the text. We, however, suspect that this was not the only outcome intended to be measured and would expect that the study would also have at least recorded adverse events. We thus deemed it likely that there was selective reporting in this study and similarly awarded this study an unclear risk of bias for reporting bias.

Other potential sources of bias

In the study by Allen 1983, participants were assessed for baseline seizure rates for an undisclosed period of time and were defined as being 'drug-resistant' although there was no description of how the diagnosis of epilepsy had been made. Participants were thus included if they were having four or more uncontrolled seizures a month. Moreover, there was no information provided as to the exact number of participants with each baseline seizure type, these being generalised-onset and focal-onset seizures, which were later described within the results taken from the two treatment periods. No exclusion criteria were presented. Additionally, there was no description of any adjustment of the dosage. Notably, however, whilst the mean serum clobazam concentration, taken during the last three weeks of treatment, was 0.33 µmol/L, there was a wide range (0.13 µmol/L to 0.99 µmol/L). This could indicate either: a wide range of participant-dependent pharmacokinetic variability, variation in compliance, or undisclosed dosage alteration. As a result, Allen 1983 was assessed to have a unclear risk of bias with regards to other sources of bias.

By contrast, Keene 1990 described well the inclusion criteria (requiring more than four seizures per month) and exclusion criteria (no history of degenerative central nervous system disorder, brain tumour or poor compliance) for the study. The period for which participants were required to have suffered more than four seizures per month, and the number of AEDs failing to control seizures, however, were not defined. Furthermore, there is no description of how the diagnosis of epilepsy was made or the medical co-morbidities, although the majority of included participants had some degree of mental retardation (17/21). Whilst the dosage adjustment regimen was comprehensively planned, no data were presented as to the proportion of participants who required dosage amendment in this way. Keene 1990, likewise, was deemed to have an unclear risk of bias originating from other sources.

For the Koeppen 1987 study, doses ranged between 10 mg/day and 40 mg/day clobazam, however, there was no clear protocol for dosage adjustment or standardisation of starting dose described. In contrast to the other studies, Koeppen 1987 did specify that epilepsy was diagnosed according to the International League Against Epilepsy guidelines although the inclusion criteria that participants must have at least three focal seizures a month was again for an undisclosed period. There was no report of the methods of recruitment, exclusion criteria or medical co-morbidities. This trial is particularly poorly standardised between the centres with regard to recruitment, exclusion criteria, randomisation and clobazam dosages. Collectively, this led to us similarly awarding Koeppen 1987 an unclear risk of bias from other sources.

By comparison to the other studies, Schmidt 1986 did utilise strict inclusion criteria. Participants had to have been attending the clinic for at least seven years and have been diagnosed with focal epilepsy, according to the International Classification of Epilepsy. Participants were defined as drug-resistant if they were still suffering with at least three seizures per month in the year preceding the trial, despite maximally tolerated doses of AED(s). Participants with progressive brain lesions and those with impaired capacity, limiting their ability to comply with treatment and record seizures accurately, were excluded. No medical co-morbidities were reported in the trial. Although the study described a slow up-titration to a maximal dose, it did not mention any methods for any adjustment of dosage, dependent on patient tolerability, upon reaching the maximum dosage. The study was therefore, likewise, assessed to have an unclear risk of bias with respect to other sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Clobazam compared to Placebo in the management of drug-resistant epilepsy

All four studies met our inclusion criteria as they were double-blind, randomised, placebo-controlled trials. The studies were

all cross-over trials, however, they utilised varying clobazam doses, varying wash-out periods between treatment arms, differing age groups, and baseline antiepileptic drugs (AEDs), and used different methodologies for the assessment of efficacy. Due to such methodological heterogeneity, as well as the unclear risk of bias associated with each study and the poor reporting of data collected, it was not possible to perform a meta-analysis of the results. A narrative summary of the included studies, with regard to efficacy, treatment withdrawal, adverse events, and quality of life data, therefore follows.

Fifty per cent or greater reduction in seizure frequency

Two of the included studies, involving a total of 47 participants, reported the outcome, 50% or greater reduction in seizure frequency (Summary of findings for the main comparison),

Of the 26 participants in the study conducted by Allen 1983, 15 (57.7%) were reported as having had a 50% or greater reduction in seizure frequency when receiving clobazam. No information was reported regarding the number of participants who had experienced a 50% or greater reduction in seizure frequency after receiving placebo. The authors did, however, perform an intention-to-treat analysis and reported that a significantly greater proportion of participants had a 50% or greater reduction in seizure frequency when receiving clobazam, compared to placebo ($P < 0.01$). Confidence intervals (95%) were not provided and there were insufficient data in the report to allow the review authors to estimate the confidence intervals or calculate the number of participants achieving the outcome during the placebo treatment arm.

The authors of Keene 1990 reported that 11/21 participants (52.4%) achieved a 50% or greater seizure reduction compared to baseline during the clobazam treatment period compared to none during the placebo period. No P value or confidence intervals were presented. Insufficient data were provided to allow us to carry out any further analysis.

No data regarding 50% or greater reduction in seizures were described in Koeppen 1987. The Schmidt 1986 authors did not report data for 50% or greater reduction in seizure frequency, but they did report that eight participants (40%) achieved 75% or greater reduction in seizure frequency. However, these data were collected only during the last month of the three-month treatment period, not across the entire treatment period. Furthermore, it was not made clear if comparisons were being made between treatment and pre-treatment periods, or between the clobazam and placebo period. Again, no information was provided about the number of participants that specifically experienced a 50% or greater reduction in seizure frequency when receiving placebo.

The evidence implies that patients are much more likely to attain a 50% or greater reduction in seizure frequency when receiving clobazam than when receiving placebo. This finding is, however, based upon the assumption that the absence of data regarding the number of participants who achieved a 50% of greater reduction in seizure frequency for the placebo arm meant that no participants achieved this outcome whilst receiving placebo. Consequently, the efficacy of clobazam has likely been overestimated.

Seizure frequency

Notably, none of the included studies separately reported the proportion of participants with focal-onset seizures, or the proportion of participants with generalised-onset seizures, that attained a 50% or greater reduction in seizure frequency. In an attempt to address the question of whether clobazam is equally as efficacious in managing both focal and generalised epilepsy, we instead extracted the mean seizure frequency for the two treatment arms, from the three included studies (involving 176 participants) that reported these data.

Allen 1983 found that mean seizure frequency was significantly lower during the clobazam treatment arm compared to during the placebo treatment arm for both focal-onset seizures (with or without secondary generalisation) and for all seizure types (clobazam versus placebo: 17.5 versus 32.4 ($P = 0.02$) and 17.0 versus 29.9 ($P = 0.002$), respectively). There was no significant difference in the mean seizure frequency between the two treatment arms for participants with generalised-onset seizures (clobazam versus placebo: 16.7 versus 24.2). The data presented for mean seizure frequency failed to include standard deviations or standard errors, hence preventing us from undertaking any further analysis. The individual frequency of seizure types was not stated, although the mean number of seizures per participant whilst in the placebo phase demonstrated a higher frequency of focal-onset seizures than generalised-onset seizures (32.4 versus 24.2, respectively).

Keene 1990 did not report seizure frequency. Data allowing any further analysis by the review authors were not reported. Whilst there were more participants with generalised- rather than focal-onset seizures (13 versus eight, respectively), on analysis of best responders, only those with focal seizures were significant responders ($P < 0.05$). Keene 1990 stated in the text that "Patients with partial seizures tended to respond better to clobazam than did those with generalized seizures, but numbers in each seizure group were small".

Koeppen 1987 presented the mean seizure frequency in graphical form, no numerical data were reported. The mean seizure reduction was reported as being near to the level of significance for participants with complex focal seizures ($P = 0.06$), the most prevalent seizure type for this study, however, no other numerical data were presented to support this. Additionally, the study did not report the mean seizure reduction for any of the other subtypes of seizures and, therefore, no comparison could be made.

The Schmidt 1986 authors reported that the mean number of all seizure types during the maintenance phase (months two to three of both treatment arms), when participants were maintained on the full dose of clobazam or placebo, was significantly lower during the clobazam treatment phase than the placebo phase (clobazam versus placebo: 10.4 versus 21.5, $P < 0.001$). An analysis of seizure subgroups found that mean number of focal-onset seizures (with or without secondary generalisation) were, likewise, significantly reduced (clobazam versus placebo: 10.4 versus 20.3, $P < 0.01$). The results for the generalised-onset seizure group were not significant, although a 100% reduction in seizure frequency was noted (clobazam versus placebo: 0 versus 1.1). During the whole study period, the number of participants suffering focal-onset seizures was greater than the number suffering generalised-onset seizures (20 versus five, respectively).

Interestingly, two of the included studies (Allen 1983; Keene 1990) that independently assessed the efficacy of clobazam against the seizure subtypes separately reported that clobazam significantly reduced the frequency of focal-onset seizures and was inef-

fective at significantly reducing the frequency of generalised-onset seizures. Likewise, the third study (Schmidt 1986) stated that clobazam did not significantly reduce the frequency of generalised-onset seizures, but, nevertheless, simultaneously reported that clobazam produced a 100% reduction in the mean number of generalised-onset seizures. Notably, in both studies by Allen 1983 and Schmidt 1986, a lower frequency of generalised seizures during the placebo phase, compared to focal-onset seizures, was recognised.

Overall, the general consensus appears to be that clobazam is more efficacious at reducing focal- rather than generalised-onset seizures, however, the slightly contradictory reports challenge and generate uncertainty about this finding. The limited amount of data provided by the studies prevented us, the review authors, from being able to either repeat their statistical analysis or conduct our own meta-analysis. If possible, this would have enabled us to reach a more conclusive finding.

Seizure freedom

Three studies, involving 175 participants, reported the outcome, seizure freedom (Summary of findings for the main comparison).

In the study conducted by Allen 1983, three participants (11.5%) were reported to be seizure-free during the clobazam treatment arm. No information was provided regarding the number of participants who were seizure-free whilst receiving placebo, and consequently, again, we can only assume that no participants were.

In contrast, Koeppen 1987 reported that 20 out of the 129 (15.5%) participants achieved seizure freedom during the clobazam arm of the experiment and clarified that no participants were seizure-free during the placebo arm.

Schmidt 1986 revealed that four (20%) participants were seizure-free during treatment with clobazam. However, these data were collected during only the last month of the three-month treatment period, not across the entire treatment period. Again, no information was provided about the number of participants that experienced seizure freedom when receiving placebo.

Collectively, the data extracted suggest that participants are more likely to attain seizure-freedom when receiving clobazam than when receiving placebo. Similarly, this finding is based upon the assumption that no participants achieved seizure-freedom whilst receiving placebo, despite that this was not specifically declared in two of the studies. Again, it is likely that the efficacy of clobazam could be overestimated in this review.

Treatment withdrawal

All four studies, including 197 participants, reported treatment withdrawal due to any reason (Summary of findings for the main comparison).

The authors of Allen 1983 reported that six participants withdrew from the study. One participant withdrew during treatment with placebo for undocumented reasons. For the remaining five participants, it is assumed that they withdrew during the clobazam treatment arm, however, the timing of the withdrawal and the reasons for withdrawal are not provided.

The withdrawal data reported by Keene 1990 states that two participants withdrew during the clobazam phase due to "severe behavioural change which did not respond to lowering the drug dosage", however, no details of these behavioural changes are documented.

In Koeppen 1987, 21 participants withdrew from treatment, of which three left the hospital and two withdrew for reasons not specified. Of the remaining 16 participants, three withdrew due to adverse events from clobazam, one due to adverse events on placebo, four due to insufficient efficacy of clobazam and eight due to insufficient efficacy of placebo. Overall, 10 participants withdrew from treatment during the clobazam arm and 11 withdrew during the placebo arm of the study.

Schmidt 1986 reported that one participant withdrew due to "non-compliance with seizure count and tablet count", however, the authors did not confirm which treatment arm this participant was primarily randomised to. As a consequence, the data are uninformative.

Overall, the evidence appears to suggest that there is only a slightly increased risk of treatment withdrawal for patients receiving clobazam, opposed to placebo.

Treatment withdrawal due to adverse events

Only two of the included studies, comprising of 150 participants, reported this outcome (Summary of findings for the main comparison).

As described earlier, Keene 1990 reported that two participants withdrew from treatment during the clobazam arm due to "severe behavioural change". In the study by Koeppen 1987, three participants withdrew due to adverse events during treatment with clobazam, compared to one participant withdrawing due to adverse events during treatment with placebo.

The evidence is very limited due to the extremely low number of events reported, but does suggest that patients are more likely to withdraw from treatment, specifically as a result of adverse events, when receiving clobazam than when receiving placebo.

Adverse events

Limited adverse events data were presented by Allen 1983 and Keene 1990. The former study, Allen 1983, did not report any specific adverse events quantitatively, however, did state that "Adverse effects occurred more often during the clobazam period". Specifically within the study, six participants required dose reduction due to adverse events during the clobazam phase, compared to two participants during the placebo phase. It was not, however, made clear whether these participants were in addition to the six who formally withdrew from the study. The only adverse events alluded to were mood changes which included: irritability, depression, and disinhibition.

Keene 1990 only acknowledged adverse events whilst describing the withdrawal of two participants during the clobazam phase. These withdrawals were due to "severe behavioural change which did not respond to a lowering of the dose". No other data were presented regarding the nature or frequency of adverse events.

The authors of Koeppen 1987 report that 36% (38/106) of participants suffered adverse events whilst on clobazam compared to 12% (13/106) on placebo. Drowsiness (71% clobazam and 16% placebo) and dizziness (26% clobazam and 6% placebo) were the adverse events most commonly reported. Notably, only three par-

ticipants withdrew from the study due to adverse events, whilst on clobazam, suggesting that the events experienced were likely mild to moderate in severity.

A large proportion of participants reporting adverse events was found by Schmidt 1986; 85% of participants complained of symptoms, mainly drowsiness (40% clobazam and 10% placebo), vertigo (35% clobazam and 5% placebo) and depression (25% clobazam and 5% placebo), whilst receiving clobazam. In contrast, 12 participants (60%) reported adverse events during the placebo treatment arm. It was not reported as to whether those suffering adverse events withdrew from the trial.

Collectively, the data presented suggest that adverse events are more frequently reported by participants when receiving clobazam compared to placebo. It is not clear what the most common adverse events were, or what the severity of these adverse events might be, however, drowsiness was the most reported adverse event across two of the studies.

Quality of life

Only the study conducted by Koeppen 1987, including 129 participants, described quality of life data. Data were assessed using the Clinical Global Impression (CGI) scale. Koeppen 1987 reported that 60% (64/106) of participants had achieved a therapeutic effect whilst on clobazam compared to 11% (12/106) on placebo. Furthermore, utilising three analogue scales they reported a significant improvement in mood state whilst in the clobazam phase ($P < 0.05$), although there was also a significant increase in drowsiness ($P < 0.05$). There was, however, no explanation of the methods used to collect and analyse these data and, notably, an intent-to-treat population was not used for this analysis.

Tolerance

The only study to attempt an assessment of tolerance was that conducted by Allen 1983 who, whilst reporting evidence of no tolerance, only attempted to assess this by comparison between the first and last four weeks of the treatment period, using a method that was not described.

In contrast, despite that neither Keene 1990 or Schmidt 1986 mentioned a formal assessment of tolerance, both studies reported that participants developed a tolerance to the antiepileptic effects of clobazam. Keene 1990 did not report the exact number of participants who developed tolerance but did state that it was "a significant number of patients", adding later that the tolerance reported, however, remained "much less frequent than that reported in the literature". Meanwhile, Schmidt 1986 specified that four of nine participants developed tolerance within the three-month treatment period.

Due to the lack of specific details provided by the studies, with regards to the methodology and the exact number of participants concerned, it is difficult to reach an overall judgement on the likelihood of patients developing tolerance after receiving clobazam.

DISCUSSION

Summary of main results

Four studies, representing 197 randomised participants, met the inclusion criteria for this review. All of the studies were randomised, double-blind, placebo-controlled, cross-over trials with two treatment periods. The reporting of important methodological factors, such as the method of randomisation and blinding, was poor. As a result, all of the included studies were judged to be at unclear risk of bias. Due to differences in the study methodology, the choice of outcomes, and the inadequate reporting of outcome data, it was not possible to summarise data in a meta-analysis and, consequently, we have summarised data in narrative form for this review.

The majority of participants recruited into three of the four studies had focal-onset seizures and, between them, the included studies tested a range of clobazam doses (as summarised in the Characteristics of included studies table). Current data suggest that, for patients with drug-resistant epilepsy, clobazam, when used as an add-on treatment, may reduce the frequency of seizures, although it was not possible to quantify precisely the treatment effect. Moreover, the evidence gathered by this review suggests that clobazam may be more efficacious in the management of focal epilepsy rather than generalised epilepsy. Adverse-events rates were higher during clobazam treatment periods, particularly for drowsiness, but current data did not precisely define the adverse-events profile of clobazam, nor the precise risk of individual adverse events. A slightly increased treatment withdrawal rate for participants when receiving clobazam was noted, including treatment withdrawal specifically due to adverse events. The development of tolerance to the antiepileptic effects of clobazam amongst participants was described in three of the included studies, however, no data were presented to support these observations. Importantly, the impact of clobazam on quality of life was not adequately assessed by the included studies either.

Overall, this review does suggest that clobazam could be beneficial to patients with drug-resistant epilepsy when utilised as an add-on therapy, however, we have not been able to generate an estimate of clobazam's efficacy or tolerability. Additionally, and most importantly, we are very uncertain that the effect that we have reported is accurate of the true efficacy of clobazam as a result of the low number of studies included in this review and the very low quality of evidence that they provided (See Summary of findings for the main comparison). This equally applies to the observations made regarding the tolerability of clobazam.

Overall completeness and applicability of evidence

We were unable to conduct a meta-analysis on the included studies as a result of methodological heterogeneity, the unclear risk of bias across studies, and the inconsistency of data reporting within the studies. Consequently, our ability to answer the original question, is clobazam an effective add-on therapy for drug-resistant generalised-onset and focal-onset seizures, with or without secondary generalisation, in adults and children, is limited. The narrative summary presented here does suggest that clobazam is effective at treating drug-resistant focal epilepsy and lacks efficacy for generalised epilepsy. This finding is, however, confounded by the limited number of participants with generalised epilepsy, recruited to the studies. Similarly, we are unable to infer whether clobazam is equally as efficacious at managing drug-resistant focal epilepsy in both adults and children because only one study, Keene 1990, included participants under the age of 18.

Within the included studies, the lack of consistency and detail in the reporting of study methods and results was recognised. This likely reflects the age of the studies as all four were conducted in the previous century. More recently, there has been a large focus

placed on the need for data dissemination, with respect to clinical trials, regarding both their methodology, their outcome findings, and their patient demographic (Brunoni 2010; Hudson 2015). The age of the included studies thus impacts our ability to make conclusions about the efficacy and tolerability of clobazam.

Quality of the evidence

All four studies were assessed to have an unclear risk of bias, largely owing to the insufficient amount of information available on the methods used by each study. Specifically, all four of the included studies failed to describe the methods used for random sequence generation and allocation concealment. We are, therefore, unsure whether selection bias might exist within the populations randomised to the first cross-over arm of each study. The unclear risk of bias across the studies is reflected in the GRADE assessment (See Summary of findings for the main comparison). Although the results reported were fairly consistent between the studies, and were well-directed to answer the original objective of the review, the narrative synthesis of the data produced imprecision in the analyses which negatively impacted the overall GRADE assessment. This collectively led to the quality of evidence being judged as very low for all four of the analysed outcomes. As a result, we are very uncertain about the accuracy of the effects observed and reported here.

Potential biases in the review process

Although, in accordance with our protocol, we have requested the trial protocols corresponding to each of the included studies, the time lag between when the review has been conducted compared to the time at which the original studies took place means that it has been very difficult to acquire any additional documents or missing data. This has, thus, greatly impacted our ability to conduct the review.

Agreements and disagreements with other studies or reviews

Other reviews, namely Robertson 1995 and Remy 1994, have similarly highlighted the increased efficacy of clobazam over placebo in managing epilepsy. Although both reviews included patients that were receiving clobazam as a monotherapy, the majority of patients were using clobazam as an add-on for polytherapy. Both reviews agreed that the main clinical indication for clobazam is as an add-on for the management of drug-resistant epilepsy, the focus of our current review.

Interestingly, both reviews demonstrated that the efficacy of clobazam is not just restricted to its short-term use, but is also observed after continued, long-term use, despite the concerns regarding tolerance. Both studies did, however, state that the incidence of tolerance amongst patients is highly variable between studies, consistent with that noted here in this review. Robertson 1995 and Remy 1994 reported that on average, 32% and 39% of patients, respectively, develop tolerance whilst receiving clobazam long term. Remy 1994 specified that tolerance usually occurs within one to six months of initiating treatment, and most commonly develops at six months. This thus emphasises that the short-term follow-up periods, characteristic of the included studies for this review, are most likely insufficient in length for tolerance to be observed. Consequently, this could lead us to underestimate the incidence of tolerance. A larger-scale, longer-term study is therefore necessary to fully determine the risk of tolerance amongst patients.

Remy 1994, nevertheless, reported that 28% of patients, almost one in three, can achieve long-term control of their epilepsy, using clobazam, without experiencing any diminished effectiveness or developing tolerance. Three reviews considered clobazam to be a tolerable drug (Montenegro 2003; Remy 1994; Robertson 1995). In agreement with our findings in this review, the most commonly reported adverse event was sedation, including drowsiness (Remy 1994; Robertson 1995). Notably, all of the reviews referenced were conducted prior to the millennium and, therefore, similar to this review, their literature base is limited to older clinical studies.

AUTHORS' CONCLUSIONS

Implications for practice

For patients with drug-resistant epilepsy, clobazam when used as an add-on treatment may potentially reduce seizure frequency but we are very uncertain about this conclusion. There are more data to support this for patients with focal-onset seizures than for patients with generalised-onset seizures. The quality of existing data is very low and it is not possible to define the size of treatment effect. The adverse events most commonly reported were drowsiness, dizziness, and vertigo, but current data do not adequately define the adverse-event profile of clobazam. Of importance, we must stress that the very low quality of evidence means that we are very uncertain about whether the effects described here are accurate of the true effectiveness and tolerability of clobazam.

Implications for research

To better inform clinical practice, we require various large-scale, multi-centre, parallel-group, randomised, controlled trials comparing clobazam with placebo, as well as other add-on treatments, for patients with drug-resistant epilepsy. Future trials should recruit a heterogeneous population with well-defined seizure and epilepsy types to allow the identification of patient factors, such as age, pathology, seizure types, and baseline antiepileptic drugs (AEDs), associated with the greatest benefit or harm. Of interest, research is increasingly being undertaken into epilepsy genetics, with regard to the factors contributing to 'drug-resistant' epilepsy and identifying for whom which particular AEDs will achieve greatest efficacy. Such investigations could potentially be included in future research into clobazam. Additionally, longer-term studies are necessary to fully assess the incidence of tolerance amongst patients.

Of particular note for clinical practice, because it has been off-patent for over 20 years, clobazam is cheaper than the newer AEDs available for use as add-on treatments for drug-resistant epilepsy. None of the studies included in this review, however, assessed cost-effectiveness, evaluation of which would need to be undertaken in any future research to inform clinical practice.

ACKNOWLEDGEMENTS

We would like to acknowledge Olivia O'Mahony, Kati Wambera, Kevin Farrell and Mary Connolly who were the review authors of the initial protocol for this review (O'Mahony 2003) which was later withdrawn in 2007.

We would like to acknowledge Graham Chan for strategising and performing the database searches for this review.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Allen 1983

Methods	**Study design:** double-blind, randomised, placebo-controlled, cross-over study (1 centre, UK) **Treatment period per arm:** 9 weeks **Washout period:** 8 weeks
Participants	**Randomised population:** 26 patients **Age mean (range):** 34 (18 to 60) years **Seizure type:** drug-resistant focal-onset seizures (with or without secondary generalisation) and generalised-onset seizures

Allen 1983 *(Continued)*

Interventions	30 mg/day clobazam nightly Placebo nightly
Outcomes	**Primary outcome** 1. Overall reduction in seizure frequency **Secondary outcomes** 1. Reduction in generalised seizures frequency (calculated from mean number of seizure types per group rather than seizures per individual) 2. Reduction in focal-onset seizures frequency 3. Proportion with > 50% reduction in seizures 4. Proportion seizure free **Safety and tolerability outcomes** 1. Drug tolerance 2. Adverse events
Notes	Data for the first and second periods of the cross-over trial were not reported separately.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "identically matched placebo capsule"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "identically matched placebo capsule"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "identically matched placebo capsule" Comment: participants would have self-reported seizure frequency and therefore acted as the outcome assessors. Study personnel would also have been blinded by matching placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: attrition was reported. Additional analysis was conducted in which patients who withdrew from treatment were included and were assumed to be non-responders, consistent with intention-to-treat.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. No outcome measures were predefined prior to the reporting of the outcome results

Allen 1983 *(Continued)*

Other bias	Unclear risk	Comment: undetailed report lacks specific information on diagnosis of epilepsy, baseline seizure type and frequency, exclusion criteria, adjustment of dosage.

Keene 1990

Methods	**Study design:** double-blind, randomised, placebo-controlled, cross-over study **Baseline period:** 4 weeks **Treatment period per arm:** 12 weeks **Washout period:** 4 weeks
Participants	**Randomised population:** 21 patients **Age mean (range):** 11 (2 to 19) years **Gender:** 10 males and 11 females **Seizure type:** drug-resistant generalised-onset seizures (13 participants), focal-onset seizures (8 participants)
Interventions	0.25 mg/kg/day to 1 mg/kg/day clobazam Placebo
Outcomes	**Primary outcomes** 1. Proportion with > 50% reduction in seizure frequency overall **Safety and tolerability outcome** 1. Laboratory tests 2. EEG recordings
Notes	Data for the first and second periods of the cross-over trial were not reported separately.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information on the randomisation method was not provided
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomly assigned into the placebo or the trial drug group. This was done by the hospital pharmacy without the patient, physician or dispensing pharmacist being aware of which group the patient had entered."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: no information on the method of blinding was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information on the method of blinding was provided

Keene 1990 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information on the method of blinding was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: attrition was reported. All randomised patients were included in the efficacy analysis conducted, although intention-to-treat was not specifically stated.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. Only one efficacy outcome was defined in the methods and reported in the results. We suspect that more outcomes, including safety outcomes such as adverse events, were measured but were not reported.
Other bias	Unclear risk	Comment: no description of how the diagnosis of epilepsy was made. No data provided regarding the participants who required dosage amendment although a dose adjustment regimen was described.

Koeppen 1987

Methods	**Study design:** multicentre, double-blind, randomised, placebo-controlled, cross-over study (Belgium, France, Germany, Italy and Spain) **Baseline:** 4 weeks **Treatment period per arm:** 12 weeks (4 weeks titration and 8 weeks maintenance) **Washout period:** 4 weeks
Participants	**Randomised population:** 129 patients **Age mean ± SD:** 33 ±12 years **Gender:** 56 males and 73 females **Seizure type:** mainly drug-resistant focal-onset seizures
Interventions	10 mg to 40 mg/day clobazam (single daily dose tablet taken in the evening) Placebo (single daily dose tablet taken in the evening)
Outcomes	**Primary Outcome** 1. Seizure frequency **Safety and tolerability outcomes** 1. EEG ratings 2. Global ratings of efficacy and safety 3. Adverse events 4. Physical examinations 5. Laboratory tests.
Notes	Data for the first and second periods of the cross-over trial were not reported separately.
Risk of bias	

Koeppen 1987 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information on the method of randomisation was provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information on the method of allocation concealment was provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: no information on the method of blinding was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information on the method of blinding was provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information on the method of blinding was provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: attrition was reported, however, intention-to-treat analysis was not conducted
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. Outcomes were not clearly defined in the methods section so it is unclear whether the outcomes were sufficiently reported.
Other bias	Unclear risk	Comment: methodology varied between centres and was not standardised. No description of exclusion criteria was reported and the description of dose escalation or dose adjustment was very limited.

Schmidt 1986

Methods	**Study design:** double-blind, randomised, placebo-controlled, cross-over study **Baseline:** **Treatment period per arm:** 12 weeks (4 weeks titration + 8 weeks maintenance) **Transition period:** 4 weeks (drug 1 gradually down-titrated whilst drug 2 concomitantly up-titrated)
Participants	**Randomised population:** 21 patients **Age mean (range):** 38 (18 to 54) years **Gender:** 9 males and 11 females **Seizure type:** drug-resistant focal-onset seizures (complex and simple focal-onset, generalised tonic-clonic seizures)
Interventions	10 mg to 40 mg clobazam 3 times/day (30 mg/day - 120 mg/day) Placebo
Outcomes	**Primary outcomes** 1. Seizure frequency

Schmidt 1986 *(Continued)*

	Safety and tolerability outcomes 1. Adverse events 2. Vital signs 3. Routine clinical chemistry studies 4. Neurological and psychiatric examinations
Notes	Data for the first and second periods of the cross-over trial were not reported separately.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information on the method of randomisation was provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information on the method of allocation concealment was provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The placebos were matched in color, size and taste."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The placebos were matched in color, size and taste."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: patients self-reported seizure frequency and adverse events, thus acting as the outcome assessors. Patients were effectively blinded by matching placebo. Study personnel would also be sufficiently blinded by the matched placebo and consequently, there should be no effect on data entry or analysis.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: one patient was excluded due to noncompliance therefore attrition was reported. Intention-to-treat analysis was not performed.
Selective reporting (reporting bias)	Unclear risk	Comment: protocol was not available. Specific outcome measures were not defined in the methods so cannot ascertain whether outcome measures are fully reported in the results section.
Other bias	Unclear risk	Comment: methods did not describe any dose adjustment upon reaching the maximum dose.

EEG: electroencephalogram
SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Andrade 2009	This study is not applicable as clobazam was used as monotherapy and not as add-on treatment.

Study	Reason for exclusion
Basu 2007	This is an open-label, unblinded trial so not applicable for inclusion.
Conry 2009	This study did not have the required 8-week standard treatment period that we stated in the protocol. Also this is a specific subtype of childhood epilepsy (Lennox-Gastaut) associated with significant cognitive impairment; it makes up < 5% of childhood epilepsies and is a very different entity.
NCT02134366	This study was prematurely terminated and no results are available for the study.
NCT02564952	This is an open-label extension study, unblinded trial with no control group so not applicable for inclusion.
NCT02565108	Both treatment groups received clobazam. The intervention group received clobazam and cannabidiol and the control group received clobazam and placebo. The study was therefore not eligible for inclusion.
NCT02726919	This is an open-label extension study, unblinded trial with no control group so was not applicable for inclusion
Semah 2014	This study is an open-label, cluster-randomised trial in patients with persistent focal seizures despite treatment with one AED. Only 3 patients received clobazam as add on treatment.
Vajda 1985	Pilot study with only a 3-day treatment period, followed by a longer-term study of 4 weeks, with no wash-out period. Only 9 participants randomised (of which 4 were later transferred to the open trial) and only preliminary results presented, incorporating open, non-randomised participants. No standard follow-up period or outcome measures. For the 5 in the randomised phase, no data presented to determine seizure frequency or 50% reduction. Full study report not published.

AED: antiepileptic drugs

APPENDICES

Appendix 1. Cochrane Register of Studies (CRS Web) search strategy

1. (clobazam* OR frisium OR urbanol OR urbanyl OR onfi):AB,KW,MC,MH,TI AND CENTRAL:TARGET

2. (monotherap* NOT (adjunct* OR "add-on" OR "add on" OR adjuvant* OR combination* OR polytherap*)):TI AND CENTRAL:TARGET

3. #1 NOT #2

4. #3 AND >25/04/2016:CRSCREATED

Appendix 2. MEDLINE (Ovid) search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials, published in Lefebvre 2011.

1. (clobazam$ or frisium or urbanol or urbanyl or onfi).tw.

2. exp Epilepsy/

3. exp Seizures/

4. (epilep$ or seizure$ or convuls$).tw.

5. 2 or 3 or 4

6. exp *Pre-Eclampsia/ or exp *Eclampsia/

7. 5 not 6

8. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.

9. clinical trials as topic.sh.

10. trial.ti.

11. 8 or 9 or 10

12. exp animals/ not humans.sh.

13. 11 not 12

14. 1 and 7 and 13

15. (monotherap$ not (adjunct$ or "add-on" or "add on" or adjuvant$ or combination$ or polytherap$)).ti.

16. 14 not 15

17. remove duplicates from 16

18. limit 17 to ed=20160425-20181009

19. 17 not (1$ or 2$).ed.

20. 19 and (2016$ or 2017$ or 2018$).dt.

21. 18 or 20

Appendix 3. ClinicalTrials.gov search strategy

Interventional Studies | Epilepsy | clobazam OR frisium OR urbanol OR urbanyl OR onfi | First posted from 04/25/2016 to 10/09/2018

Appendix 4. ICTRP search strategy

Condition: epilepsy

Intervention: clobazam OR frisium OR urbanol OR urbanyl OR onfi

Recruitment status: all

Date of registration between 25/04/2016 and 09/10/2018

Appendix 5. Original search methods for identification of studies

We searched the following databases, on 22 March 2007, for randomised trials using the search terms 'clobazam', 'seizure' and 'epilepsy'.

1. The Cochrane Epilepsy Group Specialised Register (22 March 2007)
2. The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 2)
3. MEDLINE (all prior to 22 March 2007)
4. Embase (all prior to 22 March 2007)
5. Database of Abstracts of Reviews of Effectiveness (DARE) (22 March 2007)
6. American College of Physicians Journals (22 March 2007)
7. BIOSIS (22 March 2007)

In addition we handsearched reference lists from identified trials for other relevant articles.

WHAT'S NEW

Date	Event	Description
9 October 2018	New citation required but conclusions have not changed	Conclusions are unchanged

Date	Event	Description
9 October 2018	New search has been performed	Searches updated 9 October 2018; no new studies identified for inclusion

HISTORY

Protocol first published: Issue 4, 2007
Review first published: Issue 2, 2008

Date	Event	Description
2 February 2011	New search has been performed	Searches updated 2 February 2011; no new studies identified for inclusion.
2 February 2011	New citation required but conclusions have not changed	Review updated: conclusions remain unchanged.

CONTRIBUTIONS OF AUTHORS

R. Bresnahan: systematic review of studies identified following updated search (April 2016 - October 2018) and the conduct of this review update.
K. Martin-McGill: systematic review of studies identified following updated search (April 2016 - October 2018)
J. Williamson: systematic review of studies identified following updated search (November 2012 - April 2016) and the initial conduct of this review update.
B. Michael: systematic review of studies included in the original version of the review and composition of the original document (Michael 2008). Systematic review of studies identified following updated search (November 2012 - April 2016).
A. Marson: systematic review of studies and editing of final document in original review (Michael 2008).

DECLARATIONS OF INTEREST

R. Bresnahan: none known.
K. Martin-McGill: none known.
J. Williamson: none known.
B. Michael: none known.
A. Marson: a consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool. Professor Tony Marson is part funded by National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

  This review update was supported by the National Institute for Health Research, via Cochrane Programme Grant funding to the Epilepsy Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol specified that trials with any level of blinding (double-blind, single-blind or unblinded) were eligible for inclusion in this review. However, in accordance with the methods of the previously published version of this review, by Michael 2008, we judged that only double-blind studies were eligible for inclusion. The original review protocol also stated that only participants with focal-onset seizures

should be included. This inclusion criteria was, however, expanded to also include participants with generalised-onset seizures in the previously published version of this review (Michael 2008). Again, for the purposes of the review update, we followed the methods specified by Michael 2008, and continued to include studies that contained both participants with focal- and generalised-onset seizures.

Furthermore, in contrast to the review protocol, we included the additional efficacy outcome, mean seizure reduction, Notably, none of the included studies reported the specific proportion of participants with focal-onset seizures or the specific proportion of participants with generalised-onset seizures that attained a 50% or greater reduction in seizure frequency, the outcome which we had originally intended to extract. Three of the studies, however, reported mean seizure reduction for both participants with focal-onset and generalised-onset seizures, separately. Including this additional efficacy outcome enabled us to examine whether clobazam was equally as efficacious at managing focal and generalised epilepsy.

Additionally, we altered the order of the outcomes listed in the original protocol. Notably, the protocol suggested that treatment withdrawal should be reported first, which would imply that this was the primary outcome. Instead, we reported 50% or greater seizure reduction first because this is the primary measure of efficacy and is the more important outcome that clinicians and end users would most likely be interested in. Additionally, this method of reporting, i.e. reporting efficacy outcomes prior to reporting tolerability outcomes, is more consistent with other current Cochrane Reviews.

Finally, we made small alterations to the wording of the original methods, adapted from the protocol by Michael 2007, and changed the previously suggested method for data synthesis from Peto odds ratio to Mantel-Haenszel risk ratio. All of the amendments made were to ensure that the review remained consistent with the guidelines detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The amendment of the data synthesis method from Peto odds ratio to Mantel-Haenszel risk ratio was especially important to aid the consumer's understanding of the reported findings as odds ratio is commonly misunderstood.

The term 'partial' has been replaced by 'focal', in accordance with the most recent classification of epilepsies of the International League Against Epilepsy (Scheffer 2017).

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [administration & dosage] [*therapeutic use]; Benzodiazepines [administration & dosage] [*therapeutic use]; Clobazam; Epilepsy [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans